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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/177,387	HARTLEY ET AL.	
	Examin r	Art Unit	
	Yucel Remy	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-35,52 and 89-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-35,52,89-96-98and99* is/are rejected.

7)☒ Claim(s) *97* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

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DETAILED ACTION

Claims 26, 28-35, 52 and 89-99 are pending in the application. This Office action is in response to the communications filed 27 October 2000.

Continued Prosecution Application

The request filed on 22 August 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/177,387 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

Claims 26, 28-35, 52, and newly added claims 89-93, 98 and 99 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bebee *et al.* for essentially the same reasons previously made of record in the Office actions mailed 24 June 1999 and 22 June 2000.

Claims 26, 28-35, 52, and newly added claims 89, 90, 90-96, 98 and 99 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either Kilby *et al.* or Snaith *et al.* in view of Ausubel *et al.* in further view of either Padgett *et al.* or Grose *et al.* and Hall *et al.* and Baum for essentially the same reasons previously made of record in the Office actions mailed 24 June 1999 and 22 June 2000 and further presented below.

Claims 94-96 stand rejected under 35 U.S.C. stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bebee *et al.* in view of Hall *et al.* for the reasons set forth below.

Claims 94-96 stand rejected under 35 U.S.C. 112, first paragraph for the reasons presented below.

Claim 97 stands rejected under 35 U.S.C. 112, first paragraph for the reasons presented below.

Claims 90 and 96 stand rejected under 35 U.S.C. 112, second paragraph for the reasons presented below.

Response to Arguments

Applicant has presented but a few arguments against the rejections of record. These arguments will be addressed in the rejections presented below.

Claim Objections

Claim 97 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26, 28-35, 52, and newly added claims 89-93, 98 and 99 are rejected under 35 U.S.C. 102(b) as being anticipated by Bebee *et al.* (U.S. Patent 5,434,066).

The instant claims are drawn to methods in which recombination sites are attached to a double stranded nucleic acid molecule through the use of primers with sequences which comprise said sites and an enzyme with polymerase activity.

Bebee *et al.* teach cloning of nucleic acids (DNA) by taking advantage of site-specific recombination systems. At column 4, beginning at line 56 they teach that their method requires that the target sequence has sites that are recognized by the recombinase being used and that the method, therefore, does not rely upon the presence of restriction sites to achieve the desired cloned product(s). They teach that the sites may be naturally present at the termini of a linear molecule but will more commonly be added to the target sequence via ligation or primer extension (i.e. the instant methods).

At columns 5-7, Bebee *et al.* teach several "site-specific" recombinase systems which are suitable for their methods. They identify several preferred embodiments including Int, Int/Xis, Cre, transposons, Tn3 resolvase, Flp, Hin and Cin as suitable for their recombinase based methods of cloning. These systems (and therefore the recombination sites) are exactly those recited by the instant claims. Applicant's attention is also drawn to column 9 where Bebee *et al.* discuss various att sites.

Bebee *et al.* further illustrate how primer extension methods are used to incorporate recombination sites into a target nucleic acid molecule. They teach the sequences for the specific lox P sites recognized by the Cre enzyme (see for example column 5). They also teach PCR primers #790 and #791 which include the LoxP recombination sites and the amplification of a

kanamycin resistance gene from a plasmid with said primers. They teach that as a result of PCR, a "cassette" or fragment comprising the kanamycin resistance gene flanked by loxP sites is obtained (see for example, columns 11 and 12). They further teach that this product (cassette) was ligated into another construct, indicating that as a result of PCR amplification, a double-stranded product was obtained. Bebee *et al.* do not specifically disclose specific thermostable DNA polymerases used in their PCR reactions; however, the list recited in claim 33 is fairly complete and recites some of the first commercially available enzymes such as Taq, VENT and DEEPVENT. That Bebee *et al.* did not specify the polymerase used in their PCR reaction indicates that any DNA polymerase suitable for PCR would be appropriate in their methods and that by the time of their invention, PCR protocols were well known and established to the point that one of ordinary skill in the art would have recognized and known appropriate DNA polymerases (thus Bebee *et al.* did not need to disclose that which was well known).

In the amendment filed 27 October 2000, Applicant argues that because the disclosure of Bebee *et al.* is allegedly limited to the use of Cre/*Lox*P and because the claims have been amended to exclude embodiments drawn to Cre/*Lox*P, that the rejection has been obviated. This argument has been considered, but is not found persuasive in light of the discussion immediately above. While it is true that Bebee *et al.* present examples based on the Cre/*Lox*P system, this in no way limits their teachings to said system. This is especially so in light of the fact that they identify other specific recombinases and their corresponding recombination sites as preferred embodiments and explicitly state that primer extension based methods are suitable for the addition of

recombination sites to target nucleic acid molecules. Therefore, Bebee *et al.* teach that which is recited by the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 26, 28-35 and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Shuman (U.S. Patent 5,766,891).

The instant claims have been described above.

Shuman teaches construction of chimeric nucleic acid molecules in vitro using the site-specific recombinase from Vaccinia virus. Shuman teaches that this enzyme cleaves at a consensus pyramidine element (see for example column 1). At column 6, Shuman teaches how nucleic acids are cloned using his system. He teaches the construction of bivalent nucleic acid substrates which are duplex molecules flanked by the recognition sequences for the Vaccinia (topoisomerase) recombinase enzyme. Shuman explicitly teaches the addition of the recombination sites via a primer extension method (see for example lines 46-55). He further explains this procedure at column 7, second full paragraph. Shuman clearly teaches the

production of nucleic acids to be cloned which comprise recombination sites at one or both ends wherein said sites are added via a primer extension method; thus, Shuman teaches that which is recited by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26, 28-35, 52, and newly added claims 89-96, 98 and 99 rejected under 35 U.S.C. 103(a) as being unpatentable over Bebee *et al.* as applied to claims 26, 28-35, 52, 89-93,

98 and 99 above and in further view of Hall *et al.* (Molecular Microbiology, Vol. 15 (4): 593-600, 1995).

The teachings of Bebee *et al.* have been presented above. Claims 94-96 are drawn to the methods described above in which the recombination sites are from integrons.

Hall *et al.* teach that integrons are a type of transposon (see for example page 596) which contain all the elements of site-specific recombination systems. In this teaching they also further corroborate the teachings of Bebee *et al.* who teach that transposons in general are an example of site-specific recombination systems. They further present information about a wide variety of recombination sequences (59 base-pair elements) corresponding to integrons (see pages 596-597), including the sequence of core sites. They also teach that these elements also participate in Int-mediated recombination in which two 59 base-pair elements or a single 59 base-pair element and an att site.

The ordinary artisan would have been motivated to modify the methods of Bebee *et al.* to incorporate the recombination sites of integrons as taught by Hall *et al.* The ordinary artisan would have been motivated to do so for several reasons, including flexibility and with an eye to performing multiple cloning functions simultaneously. Hall *et al.* teach that one may use unmatched recombination sites from integrons (i.e. an attL site and a 59 base-pair element). The use of multiple recombination sites/enzymes allows for simultaneous cloning. The ordinary artisan would also have had motivation to make the above modification to elucidate the relative efficiencies of different recombination enzymes and their corresponding recombination sites in the

cloning of large fragments versus smaller ones, or the cloning of nucleic acid fragments with differing secondary structures. The ordinary artisan would have had a good expectation of success absent evidence to the contrary because of the teachings of both references since both references illustrate that the art recognized transposons (of which integrons are an example) as site-specific recombination systems and that said systems are used for the manipulation of nucleic acids such as cloning. Therefore the ordinary artisan would immediately recognize the advantages of incorporating the 59 base-pair elements from integrons via primer extension into a target DNA to be cloned (recombined) into a location of interest (i.e. into a vector). Therefore, the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

Claims 26, 28-35, 52, 89-96, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilby *et al.* (Trends in Genetics, 9(12): 413-421, 1993) or Snaith *et al.* (Gene, 166:173-174, 1995) in view of Ausubel *et al.* (Current Protocols in Molecular Biology) and further in view of Padgett *et al.* (Gene, 168:31-35, 1996) or Grose *et al.* (U.S. Patent 5,710,248), Hall et al (Molecular Microbiology, 15(4):593-600, 1995) and Baum (U.S. Patent 5,650,308).

The invention of the instant claims has been described above. The grounds of this rejection are essentially those presented in the previous Office actions.

The first two references are cited because they illustrate that it was known and recognized in the art that site specific recombination facilitates cloning and engineering of nucleic acids. Kilby *et al.* present an overview of site specific recombination systems and their potential uses for

engineering of genomes. They present the sequences for specific recombination sites from the Cre/lox and the FLP/FRT systems.

Snaith *et al.* also teach the importance of the site specific recombination systems for manipulation of target nucleic acid molecules. They teach plasmids with loxP and FRT recognitions sites in their multiple cloning sites to facilitate the construction of (target) molecules for recombination. They, too, disclose the sequences for the recognition sites for both systems.

The teachings of Hall *et al.* regarding integrons representing another site-specific recombination system and the relationship of integrons to transposons were discussed above. It addition, Hall *et al.* teach the salient features of the 59 base-pair elements which are the recognition sequences/recombination sites for the integrons' integrase (recombinase) protein.

Baum is cited to illustrate that the art recognized transposons as possessing site-specific recombination activities and that these activities are harnessed for the manipulation of nucleic acids (see for example column 4). Baum teaches that transposons from Bacillus represent site-specific recombination system. He further teaches that the resolvase/recombinase of the transposon element catalyzes site-specific recombination events on (nucleic acid) comprising two copies of resolution sites (see columns 10-12). He also teaches that said sites can be from a Tn3-type transposon, which is known in the art to have a resolvase, but that such sites from other sources would also function (see for example column 13).

None of the references above disclose the introduction of recombination sites via a PCR based method (primer extension-based method) to a nucleic acid molecule. The references either

do not disclose how the sites are incorporated or they disclose other, equivalent methods such as cloning and ligating fragments with the appropriate sites to the molecules of choice.

Ausubel *et al.* teach various PCR-based methods for introducing modifications (any desired sequence change) to nucleic acids (see 8.5.1). They teach PCR methods (primer extension) in which a desired restriction site is incorporated into a desired nucleic acid using appropriate primers and Taq polymerase.

Padgett *et al.* and Grose *et al.* are cited to illustrate that the methods taught by Ausubel *et al.* function to incorporate any desired sequence into any nucleic acid. Padgett *et al.* teach PCR methods to incorporate a specific recognition site for a specific enzyme, Eam1104I. They teach the introduction of their sites at or near the termini of their fragments using appropriate primers and Taq polymerase.

Grose *et al.* teach a recombination site specific PCR mutagenesis technique in which a specific stretch of 24 nucleotides were inserted into a gene using "mutating primers" (see for example column 3). Grose *et al.* teach the incorporation of a specific tag into a nucleic acid of interest (see for example columns 7-9, 13 and 14), further illustrating that, at the time of the invention, it was well known to use PCR-based methods to incorporate desired sequences (for example, recognition sites or tags) into specific locations of target nucleic acid molecules of interest.

It was well known well before the time of the invention that restriction sites are recognition sequences for restriction endonucleases which are proteins with enzymatic activities.

It is appropriate here to review Applicant's own definitions of "recognition sequences" and "recombination sites". At page 22, line 30 to page 23, line 19, Applicant sets forth definitions for these terms. Applicant defines "recognition sequences" as "particular sequences which a protein, chemical compound, DNA, RNA molecule (e.g. restriction endonuclease, a modification methylase, or a recombinase) recognizes and binds. In the present invention, a recognition sequence will usually refer to a recombination site. For example, the recognition sequence for Cre recombinase...." In this passage, Applicant enumerates other recognition sequences for other recombinases. It is abundantly clear from Applicant's own specification that "recombination sites" are "recognition sequences".

Given the teachings of the prior art discussed immediately above, the ordinary artisan would have been motivated to incorporate recombinase recognition (recombination) sequences into a nucleic acid of interest (DNA or RNA) because of the teachings of Kilby *et al.*, Snaith *et al.* Hall *et al.* and Baum who teach various site specific recombination systems and their advantages for molecular engineering (cloning).

The ordinary artisan would have been further motivated to use primer extension-based techniques taught by Ausubel *et al.* and exemplified by Padgett *et al.* and Grose *et al.* for introducing the recognition (recombination) sites of interest. Ausubel *et al.* teach that **any** sequence may be introduced via such methods, including restriction sites. This teaching, as well as the demonstration of Padgett *et al.*, speaks directly to the crux of the claimed invention--which

is the introduction of recognition sites for recombinase enzymes into a nucleic acid via primer extension based methods. Restriction sites, which are recognition sites for restriction enzymes, clearly are analogous to the recognition sites for the recombinase enzymes of the instant invention. This observation is completely corroborated by Applicant's own specification as discussed immediately above.

The ordinary artisan would have also recognized that, by using primer extension (PCR) methods for said introduction, the recognition sites for the recombinase enzymes could be inserted at precise locations of the nucleic acid molecule, independent of the presence of appropriate restriction sites for cloning.

Furthermore, absent evidence to the contrary, the ordinary artisan would have a good expectation of success of using such methods for incorporation of specific recognition (recombination) sequences (as taught by Kilby *et al.*, Snaith *et al.*, Hall *et al.* or Baum) because of the teachings of Padgett *et al.* and Grose *et al.* who demonstrate incorporation of desired sequences, such as recognition sequences for endonucleases, as per the teachings of Ausubel *et al.* Thus, the invention, as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

In the remarks submitted 27 October 2000, Applicant argues that the Hartley *et al.* reference is not available as prior art under 35 U.S.C. 103(c) (pages 7-9). This argument is persuasive and as such, the reference is now no longer included in the rejection. The balance of Applicant's arguments present a piecemeal analysis of the remaining references and allege that the

Examiner has not met her burden of establishing a *prima facie* case of obviousness. These arguments have been considered but are not found persuasive.

First, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The first paragraph on page 9 presents a circular argument which ignores the fact that the rejection of record was and is based on the combination of teachings of the references and as such, the argument remains unpersuasive.

The balance of Applicant's argument appears to be a boilerplate response to a rejection under 35 U.S.C. 103. The sentence bridging pages 9 and 10 is in direct contradiction to the second sentence of the second complete paragraph found at page 9. It is well established that the teaching or suggestion need not be limited to that which is in the cited references, but may properly come from "*the knowledge generally available to one of ordinary skill in the art would lead that individual to combine relevant teachings of the references....*".

Applicant's second sentence on page 10 is particularly unpersuasive. There was no "attempt" to analogize recombination sites with restriction sites, because none was needed. It was well known in the art even before the time of the invention, that both restriction and recombination sites are recognition sequences which are acted upon by various enzymatic proteins (see Kilby, Snaith, Hall, Baum and Ausubel). With all due respect to Applicant, it does not take a

tremendous skill level to recognize the similar and analogous nature of recombination and restriction sites which represent subsets of recognition sites as a whole. It is also noted that Applicant's own disclosure identifies "recombination sites" and "restriction sites" as "recognition sequences". The rejection previously made of record and the one presented above clearly presents the teachings of the references, provides motivations to combine the teachings as well as the basis for the expectation of success. Thus, Applicant's contention that the Examiner has not met her burden remains unpersuasive.

In fact, the burden now rests with Applicant to provide evidence to the contrary that every sequence **but** those for recombination sites are amenable to primer extension methods. Is there something special about these sites that they are recalcitrant to being manipulated by primer extension methods? Clearly this is not the case. Is there some other evidence which would lead the ordinary artisan to expect utter failure in using primer extension methods to attach recombination sites which are enzyme recognition sites to a nucleic acid, especially in light of the fact that the very same methods were used to introduce other enzyme recognition sites to nucleic acid molecules (see for example Padgett *et al.*)? This also does not appear to be the case. As such, the arguments presented by Applicant remain unpersuasive in the context of the rejection presented above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90, 93, 94 and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 90, the distinction amongst "mutants", "variants" and "derivatives thereof" is not clear. The specification does not appear to set forth specific definitions for these terms which are regarded as equivalents in the art. The recitation "derivatives" poses a further problem because the nature and number of derivative processes is not defined. As a result the metes and bounds of the claim cannot be established. Further, the use of plural forms in this claim further render it vague and indefinite because it is not clear which "mutants", "variants" and "derivatives" are encompassed by the claim.

In claims 93 and 94, it is not clear if Applicant intends for the recombination sites to be comprised of the entire transposon or transposable genetic elements or only those portions which contain the recognition sites for the transposase. Applicant is cautioned that if it is the latter, then issues under enablement could be raised.

Claim 96 depends from itself.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official

Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6 (d)). The Group 1600 FAX numbers are (703) 308-4242 or (703) 305-3014. Unofficial faxes may be sent to the examiner at (703) 305-7939. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph. D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday through Fridays from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388.

Remy Yucel, Ph. D.
Primary Patent Examiner
Technology Center 1600
January 16, 2001